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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,631	04/11/2005	Seiichi Araki	T0509.70011US00	5167

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EXAMINER	
HUGHES, ALICIA R	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
12/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/506,631	**Applicant(s)** ARAKI ET AL.	
	Examiner ALICIA R. HUGHES	**Art Unit** 1614	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 October 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *15 and 19*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Raymond J Henley III/
Primary Examiner, Art Unit 1614

Continuation of 3. NOTE: Applicants have amended the claims to reflect the administration of riboflavin sodium phosphate or flavin adennine dinucleotide rather than the myriad of other forms of riboflavin and riboflavin derivatives. Neither riboflavin sodium phosphate nor flavin adennine dinucleotide were contemplated for search individually at the time claims were filed during prosecution. Their consideration now would require a new search .

Continuation of 11. does NOT place the application in condition for allowance because: Grimble teaches that antioxidative vitamins such as riboflavin prevent increased cytokine production via the glutathione production pathway. One of ordinary skill in the art would have found it obvious that a reduction in cytokines would be efficacious in the treatment of hypercytokinemia. The use of a salt of riboflavin would have been obvious to one of ordinary skill in the art since salts dissociate and a salt of riboflavin would naturally dissociate into riboflavin and the salt.

At the time the present invention was disclosed, it was well-known in the art that there is a direct correlation between the functionality of balanced cytokine production when reacting to an inflammatory response and the activity of the glutathione production pathway to limit the creation of excessive cytokines. It has been known for quite some time that "[c]ytokines play a crucial role as modulatory agents by which the activity of the system is changed and metabolic activity of the host directed towards provision of nutrients for the system from endogenous sources. Nutrient intake, prior to infection will influence the extent of endogenous nutrient provision." Id. Glutathione is defined as a "major endogenous antioxidant," and "[v]itamin B6 and riboflavin participate in the maintenance of glutathione status" (See Abstract). Thus, endogenous nutrient provision, i.e. glutathione production, controls hyperactivity of cytokines, or hypercytokinemia, and "[v]itamin B6 and riboflavin participate in the maintenance of glutathione status" (See Abstract).

In short, "[d]eficiencies in vitamins E, B6 and riboflavin reduce cell numbers in lymphoid tissues of experimental animals and produce functional abnormalities in the cell mediated immune response." Id. Thus, where there is a deficiency is riboflavin, endogenous nutrient provision provided by glutathione will lack, thereby creating a heightened immne/inflammatory response that wields the over- or hyper-production of cytokines. Therefore, if a deficiency in riboflavin contributes to a heightened inflammatory response then it logically flows mechanistically that the presence of riboflavin has an inverse relationship with cytokine production as an immune response. It is the establishment of this relationship that makes the prior art rejection in Grimble, et al applicable to the instant invention.

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